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		First Named Inventor	Milton David GOLDENBERG
		Art Unit.	1618
		Examiner Name	HARTLEY, Michael G.
Total Number of Pages in This Submission		Attorney Docket No.	40923-0126 US3 [1094]

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Date	September 26, 2005

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Attorney Docket No.: 40923-0126 US3 [1094]
(18733-1094)

In re patent application of:
Milton D. Goldenberg

Confirmation No.: 8273

Application No.: 10/086,637

Art Unit: 1618

Filing Date: March 4, 2002

Examiner: Michael G. Hartley

For: Intraoperative Intravascular And Endoscopic Tumor And Lesion Detection, Biopsy And Therapy.

REPLY BRIEF

Mail Stop Appeal Brief - Patents
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Heller Ehrman LLP

REPLY BRIEF

I. TIMING OF FILING

This Reply Brief is being filed within two months of the Examiner's Answer dated July 28, 2005. No fees are believed due.

II. GROUNDS OF REJECTION MAINTAINED ON APPEAL

1. Claims 183,187-189,191-193, 196 and 197 stand rejected under 35 USC § 103 (a) as being obvious over Goldenberg (U.S. Patent No. 4,932,412) ("Goldenberg") in view of Barbet (U.S. Patent No. 5,256,395) ("Barbet").

2. Claim 190 stands rejected under 35 USC § 103 (a) as being obvious over Goldenberg in view of Barbet in further view of Horowitz (U.S. Patent No. 4,706,652) ("Horowitz").

III. REPLY TO EXAMINER'S ANSWER

A. The Examiner's Concession

Appellants argued in their Appeal Brief that the Examiner's obviousness rejection over Goldenberg (U.S. Patent No. 4,932,412) ("Goldenberg") in view of Barbet (U.S. Patent No. 5,256,395) ("Barbet") was flawed as a matter of fact. The flaw was in the Examiner's interpretation of Goldenberg: Goldenberg didn't teach everything the Examiner said it did. In the Examiner's Answer, the Examiner agreed with this assertion. Specifically, the Examiner stated:

> Appellant asserts that Goldenberg does not teach all that the examiner states, that is Goldenberg does not teach all the elements except that hapten system. Appellant asserts that Goldenberg only shares the preamble with claim 183.

> Part of this argument is agreed upon. Goldenberg is used mainly to show the same method, as disclosed in the preamble of claim 183, is know in the art.

Examiner's Answer, page 6, last two paragraphs.

The preamble to which the Examiner refers, is as follows:

183. A method of close-range detection of lesions during an operative, endoscopic, laparoscopic, intravascular catheter, or surgical procedure, wherein the method ....

The Examiner explicitly equates Goldenberg's teachings with this preamble. However, the above preamble does not direct one towards the steps that follow it. Nothing in this preamble suggests the following steps recited in claim 183:

> (a) injecting a patient who is to undergo such a procedure with a bispecific antibody fragment or subfragment with a molecular weight of 85,000 daltons or less, wherein the bispecific antibody fragment has a first antibody binding site which specifically binds to an antigen produced or associated with a lesion, and has a second antibody binding site which specifically binds to a hapten, and permitting the antibody fragment to accrete at target sites;
>
> (b) injecting a bivalent labeled hapten, which quickly localizes at the target site and clears through the kidneys; and
>
> (c) detecting the presence of the hapten by close-range detection of elevated levels of accreted label at the target sites with detection means, within 48 hours of the first injection, and conducting said procedure.

In their Appeal Brief, Appellants painstakingly analyzed each element recited in steps a) - c) and explained how Goldenberg not only didn't suggest any of the recited steps but was concerned with an entirely different process. Thus, Appellants assert now- and the Examiner should agree- that Goldenberg is not relevant to the invention of claim 183.

B. The Examiner's Reliance upon Barbet

The Examiner now explains that Barbet provides all of the steps missing from Goldenberg. Arguably, if one were to follow the Examiner's logic and arguments, any radioimmumodiagnostic method using bi-specific antibodies and labeled haptens would have been obvious over Barbet's teachings because, according to the Examiner, Barbet teaches that its methods improve effectiveness. The problem with this line of reasoning is two-fold. First, it ignores the nature of Barbet's teachings and second, it ignores the specific limitations in the claims.

Barbet teaches the basic science related to constructing hapten reagent systems. In columns 8 and 9, it prophetically describes procedures for using the reagents *in vivo*. This prophetic description is general. It describes the need for "adjustments" related to dosage and timing. However, all Examples relate to *in vitro* testing of various conjugates. Barbet does not mention or suggest close-range detection of lesions during an operative, endoscopic, laparoscopic, intravascular catheter, or surgical procedures.

Claim 183 recites a method specific for close-range detection of lesions during an operative, endoscopic, laparoscopic, intravascular catheter, or surgical procedures and the steps include specifics with regard to the type of antibody (divalent, single chain fragment or subfragment), the size of the antibody (less than 85,000 daltons), and type of hapten (bivalent, labeled) and the timing of the detection (within 48 hours of first injection). Although Barbet teaches the preparation of a variety of hapten reagents (some with one antibody, some with two antibodies, some fragments, some whole monoclonals, some with one hapten, some with two haptens) and lists a multitude of radiolabels and various toxins, it doesn't direct the skilled artisan to the specific elements recited in claim 183.

C. The Examiner's Selective Reading of the Art

The Examiner arrives at the specific recitations in claim 183 by "picking and choosing" teachings from Goldenberg and Barbet. For instance, the Examiner points out that Barbet teaches antibody fragments at col. 6, lines 25-36 and Goldenberg also teaches that the use of antibody fragments is common place in radioimmuno-diagnostics. (Examiner's Answer at page 8, middle paragraph). However, the type of antibody used in Goldenberg is not relevant to the rest of Goldenberg's teachings. Appellants discussed this in detail in their Appeal Brief at pages 8-10. Similarly, the type of antibody used in Barbet is not relevant to the rest of what Barbet teaches. Barbet suggests using all sorts of antibodies and antibody fragments. Although both Goldenberg and Barbet acknowledge the possible use of antibody fragments, some of which may be less than 85,000 daltons, neither document directs the skilled artisan to using such antibodies and neither document directs one towards their use in the close range detection method of claim 183. Neither Goldenberg nor Barbet is concerned with such a method.

Neither Goldenberg nor Barbet directs the skilled artisan towards detecting a hapten by close-range "within 48 hours of injecting a bispecific antibody." Contrary to the Examiner's explanation for relying upon Goldenberg, Goldenberg's teachings are simply not relevant to the invention of claim 183. Goldenberg describes a different process with different goals and different steps. The Examiner partially agrees that his reliance upon the time frames in Goldenberg is like comparing apples to oranges (Examiner's Answer at page 9) but continues to pursue this line of reasoning, nevertheless.

Although Barbet's teachings are relevant, they are very general. They relate to any and all immunodiagnostic methods that use hapten-based reagents. Barbet's teachings are best characterized as inviting experimentation. Barbet sets forth all the relevant variables and tells the reader to figure it out. It says "imaging may be performed a few hours after injection of the affinity enhancement probe, at a time when

optimum localization has been achieved. This time may be selected according to the pharmacokinetic properties of the affinity enhancement probe, the radioactive decay of the isotopes and the rate at which the affinity enhancement probe is able to localize at the specific target site." Column 9, lines 5-14. Although Barbet provides a myriad of possibilities, it doesn't provide guidance toward the specifically claimed invention.

D. Combinations.

In the Examiner's Answer (page 10), the Examiner faults Appellants for not considering the art "in combination". However, Appellants argue that Goldenberg should not be cited at all: it is not relevant to the claimed invention. It is a red-herring. One reading Goldenberg would not view it as a one step process that could be improved with a two step process, as the Examiner has argued. Goldenberg is related to method of reducing background radiation. Appellants discuss this in detail in their Appeal Brief. at pages 8-12. Contrary to the Examiner's position, one reading Goldenberg would not have been motivated to combine its teachings with Barbet.

Barbet is relevant for teaching a background technology (hapten reagents) that is applicable to the claimed invention. However, Barbet's teachings are very broad and, with regard to *in vivo* applications, prophetic. As such, Barbet invites experimentation. It doesn't guide the artisan towards the method of claim 183 or the teachings of Goldenberg, if Goldenberg were, in fact, relevant.

E. Claim 190

In the Examiner's Answer, the Examiner maintains the rejection of Claim 190 as obvious over Goldenberg in view of Barbet in further view of Horowitz (U.S. Patent No. 4,706,652) ("Horowitz"). Claim 190 depends from claim 183 and recites that the method further comprises the step of administering brachytherapy via the endoscope or catheter to lesions at sites of elevated label secretion. The Examiner cites Horowitz for

teaching that brachytherapy, by administering radioactive seeds via a catheter, provides the advantage of safer implants that allow the patient to be discharged.

Appellants again rely upon the above arguments with regard to Goldenberg and Barbet to address the rejection of claim 190. Horowitz does not cure the deficiencies in the Examiner's case with regard to the primary references.

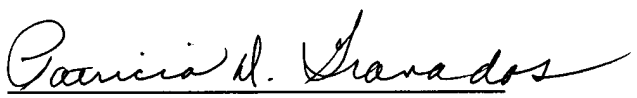
F. Double Patenting

Appellants thank the Examiner for agreeing to hold the double patenting rejection in abeyance.

* * *

In view of the above arguments and evidence of record, Appellants respectfully request the Board to reverse the Examiner's rejection of claims.

Respectfully submitted,



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IV. CLAIMS APPENDIX (FOR REFERENCE ONLY)

183. A method of close-range detection of lesions during an operative, endoscopic, laparoscopic, intravascular catheter, or surgical procedure, wherein the method comprises:

(a) injecting a patient who is to undergo such a procedure with a bispecific antibody fragment or subfragment with a molecular weight of 85,000 daltons or less, wherein the bispecific antibody fragment has a first antibody binding site which specifically binds to an antigen produced or associated with a lesion, and has a second antibody binding site which specifically binds to a hapten, and permitting the antibody fragment to accrete at target sites;

(b) injecting a bivalent labeled hapten, which quickly localizes at the target site and clears through the kidneys; and

(c) detecting the presence of the hapten by close-range detection of elevated levels of accreted label at the target sites with detection means, within 48 hours of the first injection, and conducting said procedure.

184. The method of claim 183, further comprising after step (a), the step of injecting said patient with a clearing composition comprising an agent to clear circulating said bispecific antibody.

185. The method of claim 184, wherein said clearing composition comprises an anti-idiotype antibody.

186. The method of claim 185, wherein said anti-idiotype antibody is conjugated to a galactosyl residue.

187. The method of claim 183, wherein said antigen produced or associated with a lesion is a tumor- or pathogen-associated antigen.

188. The method of claim 183, further comprising the step of removing lesions at sites of elevated label accretion with a laser therapy, brachytherapy, chemo immunotherapy, radio immunotherapy, photodynamic therapy, external beam irradiation or surgical removal.

189. The method of claim 183, further comprising the step of treating lesions at sites of elevated label accretion with ionizing radiation.

190. The method of claim 183, wherein the procedure is selected from the group consisting of an endoscope, laparoscope, and intravascular catheter procedures, further comprising the step of administering brachytherapy via the endoscope or catheter to lesions at sites of elevated label accretion.

191. The method of claim 183, wherein the lesion is selected from the group consisting of a cancer, an infectious lesion, an inflammatory lesion, a non-tumorous lesion, a clot, hyperplasia and atherosclerotic plaque.

192. The method of claim 183, wherein said procedure is a laparoscopic procedure.

193. The method of claim 183, wherein said hapten is labeled with a diagnostic radioisotope, a MRI image enhancing agent or a fluorescent label.